Complete Summary

GUIDELINE TITLE

Treatment of primary headache: preventive treatment of migraine. Standards of care for headache diagnosis and treatment.

BIBLIOGRAPHIC SOURCE(S)

Kaniecki R, Lucas S. Treatment of primary headache: preventive treatment of migraine. In: Standards of care for headache diagnosis and treatment. Chicago (IL): National Headache Foundation; 2004. p. 40-52. [6 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- On September 30, 2004, Vioxx (rofecoxib) was withdrawn from the U.S. and worldwide market due to safety concerns of an increased risk of cardiovascular events. See the U.S. Food and Drug Administration (FDA) Web site for more information.

  Subsequently, on April 7, 2005, after concluding that the overall risk versus benefit profile is unfavorable, the FDA requested that Pfizer, Inc voluntarily withdraw Bextra (valdecoxib) from the market. The FDA also asked manufacturers of all marketed prescription nonsteroidal anti-inflammatory drugs (NSAIDs), including Celebrex (celecoxib), a COX-2 selective NSAID, to revise the labeling (package insert) for their products to include a boxed warning and a Medication Guide. Finally, FDA asked manufacturers of non-prescription (over the counter [OTC]) NSAIDs to revise their labeling to include more specific information about the potential gastrointestinal (GI) and cardiovascular (CV) risks, and information to assist consumers in the safe use of the drug. See the FDA Web site for more information.

  Most recently, on June 15, 2005, the FDA requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labeling changes to their products. FDA recommended proposed labeling for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including Celebrex (celecoxib), a COX-2 selective NSAID, have been asked to revise the

labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for products that FDA determines pose a serious and significant public health concern. See the FDA Web siteFDA Web site for more information.

Additional Notices

- On February 15, 2006, Bayer and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of changes to the prescribing information for nimodipine (Nimotop), including a boxed warning to notify prescribers about medication administration errors. When administered intravenously or parenterally, it can cause serious adverse events, including death. Nimodipine must not be administered intravenously or by any parenteral route. See the FDA Web site for more information.
- On December 8, 2005, the U.S. Food and Drug Administration (FDA) has determined that exposure to paroxetine in the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiac malformations. At the FDA's request, the manufacturer has changed paroxetine's pregnancy category from C to D and added new data and recommendations to the WARNINGS section of paroxetine's prescribing information. FDA is awaiting the final results of the recent studies and accruing additional data related to the use of paroxetine in pregnancy in order to better characterize the risk for congenital malformations associated with paroxetine.

  Physicians who are caring for women receiving paroxetine should alert them to the potential risk to the fetus if they plan to become pregnant or are currently in their first trimester of pregnancy. Discontinuing paroxetine therapy should be considered for these patients. Women who are pregnant, or planning a pregnancy, and currently taking paroxetine should consult with their physician about whether to continue taking it. Women should not stop the drug without discussing the best way to do that with their physician. See the FDA Web site for more information.

- On September 27, 2005, GlaxoSmithKline (GSK) and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of changes to the Pregnancy/PRECAUTIONS section of the Prescribing Information for Paxil and Paxil CR Controlled-Release Tablets to describe the results of a GSK retrospective epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy. This study suggested an increase in the risk of overall major congenital malformations for paroxetine as compared to other antidepressants [OR 2.2; 95% confidence interval, 1.34-3.63]. Healthcare professionals are advised to carefully weigh the potential risks and benefits of using paroxetine therapy in women during pregnancy and to discuss these findings as well as treatment alternatives with their patients. See the FDA Web site for more information.
- On February 18, 2005, the U.S. Food and Drug Administration (FDA) announced that a bolded Warning will be added to the labeling for Gabitril

(tiagabine) to warn prescribers of the risk of seizures in patients without epilepsy being treated with this drug. Although Gabitril has been shown to reduce the frequency of seizures in patients with epilepsy, paradoxically, Gabitril's use has been associated with the occurrence of seizures in patients without epilepsy. Gabitril is approved for use only as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures. Because Gabitril has not been systematically evaluated in adequate and well-controlled trials for any other indication, its safety and effectiveness have not been established for any other use. Cephalon will undertake an educational campaign to discourage off-label use of Gabitril. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Migraine headache

GUIDELINE CATEGORY

Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology

INTENDED USERS

Health Care Providers
Physicians

GUIDELINE OBJECTIVE(S)

- To improve the medical treatment of headache
- To help physicians and other health care professionals to:
    - Design a treatment plan, combining nonpharmacologic with pharmacologic approaches as necessary to:
        - Minimize symptomatology
        - Reduce disability
        - Improve quality of life
    - Provide follow-up care for long-term headache management to:
        - Reassess how well the treatment plan is achieving established goals
        - Reevaluate patient needs and specific headache patterns

TARGET POPULATION

Migraine patients with the following clinical presentations:

- Headache frequency more than 2 days per week (or >8 days/month)
- Use of acute medications, successfully or unsuccessfully, more than 2 days per week
- Headache attacks that remain disabling despite aggressive acute intervention, as documented by lifestyle interference, ratings on disability scales, or use of rescue medications more than once a month
- Presence of prolonged aura (>1 hour), complex aura (basilar or hemiplegic), or migraine-induced stroke
- Contraindications to, failure of, overuse of, or adverse events with acute therapies
- Patient desire to reduce frequency of acute attacks

INTERVENTIONS AND PRACTICES CONSIDERED

1. Beta-blockers
    - Atenolol
    - Metoprolol
    - Nadolol
    - Propranolol
    - Timolol
2. Calcium antagonists
    - Diltiazem
    - Nimodipine
    - Nicardipine
    - Verapamil
3. Neurostabilizers
    - Divalproex sodium
    - Gabapentin
    - Tiagabine
    - Topiramate
4. Nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Acetylsalicylic acid
    - Celecoxib
    - Fenoprofen
    - Flurbiprofen
    - Ketoprofen

- Nabumetone
- Naproxen
- Rofecoxib

5. Tricyclic antidepressants
    - Desipramine
    - Protriptyline
    - Amitriptyline
    - Doxepin
    - Imipramine
    - Nortriptyline
6. Selective serotonin reuptake inhibitors (SSRIs)
    - Fluoxetine
    - Fluvoxamine
    - Paroxetine
    - Sertraline
7. Other antidepressants
    - Bupropion
    - Nefazodone
    - Trazodone
    - Venlafaxine
8. Special-use therapies
    - Methylergonovine
    - Phenobarbital + ergotamine tartrate + belladonna alkaloids
    - Cyproheptadine
    - Methysergide
    - Monoamine oxidase inhibitors (i.e., phenelzine)
    - Botulinum toxin type A
    - Feverfew
    - Magnesium
    - Petasites hybridus extract
    - Riboflavin (vitamin B_2)

MAJOR OUTCOMES CONSIDERED

- Effectiveness of medications in reducing frequency of migraine attacks
- Side effects of medications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The guidelines presented in this monograph represent the consensus of an advisory panel of practitioners chosen by the National Headache Foundation (NHF) for their expertise. In addition to incorporating the US Headache Consortium's recommendations, their conclusions reflect clinical experience and the most recent medical literature.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Preventive Treatment of Migraine

Most migraineurs can be effectively treated with various acute headache medications and nonpharmacologic strategies including lifestyle regulation, stimulant reduction, and trigger avoidance. However, the following clinical presentations warrant the introduction of a pharmacologic agent to reduce the frequency, duration, and severity of migraine attacks:

- Headache frequency more than 2 days per week (or >8 days/month)
- Use of acute medications, successfully or unsuccessfully, more than 2 days per week
- Headache attacks that remain disabling despite aggressive acute intervention, as documented by lifestyle interference, ratings on disability scales, or use of rescue medications more than once a month
- Presence of prolonged aura (>1 hour), complex aura (basilar or hemiplegic), or migraine-induced stroke
- Contraindications to, failure of, overuse of, or adverse events with acute therapies
- Patient desire to reduce frequency of acute attacks

Women of childbearing age require particular attention. Be sure to inform these patients of all potential risks and to select medications that will have the least adverse effect on the fetus. For pregnant patients, migraine attacks must be severe and disabling, and accompanied by nausea, vomiting, and possibly dehydration, before preventive pharmacologic treatments can be considered.

The Treatment Process

Patients should be involved in the treatment process. Their preferences about cost, drug delivery, dosing schedule, and tolerability should be considered when choosing a course of action. In addition, educating patients about the goals, use, and appropriate expectations of migraine preventive therapies is crucial to maximizing the chance for therapeutic success. Patients must understand that these therapies may reduce the frequency or severity of attacks, may improve the efficacy of acute medications, and may assist with the management of comorbid conditions but that they rarely result in complete eradication of headaches. In fact, preventive medications are considered effective if the frequency of attacks is reduced by more than 50%.

A basic principle of preventive treatment is to start the drug at a low dose and increase the dose slowly. Migraine patients often require a dose of a preventive medication that is lower than would be used for other indications. The need for compliance with the program must be emphasized, as the drug dose is generally titrated up over a few weeks and then sustained for 4 to 8 weeks before potential benefit may be realized. Most clinicians recommend a 6 to 12-month maintenance phase once a greater than 50% reduction in headache frequency has been achieved, followed by a tapering phase. To ensure optimal benefit from the

prophylactic drug, have patients track their progress with the use of a headache diary and encourage them to avoid using acute headache medications, analgesics, decongestants, and stimulants more than 2 days per week.

Treatment Strategies

Preventive treatment strategies fall into 3 basic categories: episodic, short-term, and chronic. Preventive episodic treatment should be considered if the headache trigger is known. For example, if exercise often leads to an attack, the patient can be instructed to treat prior to the activity. Short-term prevention is used when exposure to the trigger is time-limited, such as flying at high altitudes or menstruation. Treatment with daily medication just before and after exposure has been shown to be effective. For longer-term needs, chronic treatment can be used for months or years.

Pharmacologic Agents

The major classes of agents available for migraine prevention include beta-adrenergic blockers, antidepressants, anticonvulsants (now commonly called neurostabilizers), calcium antagonists, nonsteroidal agents, and serotonin receptor antagonists. The selection of a drug should be based first on efficacy, with consideration given to comorbid psychiatric or medical disease, patient preference, and patient compliance. The US Headache Consortium has published evidence-based medication guidelines following analysis of nearly 300 controlled trials of drugs used to prevent migraine (see the tables below). These guidelines assist clinicians in the selection of appropriate migraine preventive therapy by ranking drugs according to clinical efficacy, adverse events and safety, and clinical experience.

US Headache Consortium Guidelines for Migraine Prophylaxis	
Group 1 Medium to high efficacy, good strength of evidence, mild to moderate side effects	• Amitriptyline (10-150 mg/day) • Divalproex sodium (125-200 mg/day) • Timolol (10-30 mg/day) • Propranolol (20-160 mg/day) • Topiramate (50-150 mg/day)[a]
Group 2 Lower efficacy, limited strength of evidence, mild to moderate side effects	• Aspirin (325 mg/day) • Atenolol (25-100 mg/day) • Fenoprofen (600 mg three times a day [tid]) • Flurbiprofen (1,000 mg bid-tid) • Fluoxetine (10-80 mg/day) • Gabapentin (300-2,400 mg/day) • Ketoprofen (75 mg tid) • Metoprolol (50-200 mg/day) • Nadolol (20-120 mg/day) • Naproxen (200-550 mg two times a day [bid]) • Nimodipine (30 mg tid) • Verapamil (120-480 mg/day • Botulinum toxin type A (25-100 units/3

US Headache Consortium Guidelines for Migraine Prophylaxis	
	months)[a]
Group 3 No scientific evidence of efficacy, but clinically efficacious based on consensus of experience a. Low to moderate adverse events b. Frequent or severe adverse events (or safety concerns); complex management issues	• Cyproheptadine • Antidepressants such as nortriptyline, paroxetine, venlafaxine, doxepin, sertraline, and phenelzine • Methylergonovine
Group 4 Medium to high efficacy, good strength of evidence, but side effect concerns	• Methysergide
Group 5 Evidence indicating no efficacy over placebo	• Acebutolol • Pindolol • Carbamazepine • Nicardipine • Nifedipine • Indomethacin
[a] Based on evidence not available at the time of Guideline publication	

Guidelines for Selected Prophylactic Therapies in the Treatment of Migraine (see Table 4.2 in the original guideline document for doses and clarifications)	
MEDICATION	US HEADACHE CONSORTIUM GUIDELINES
Beta-Blockers	
Beta-blockers with partial agonist activity have not been shown to have efficacy in migraine prophylaxis	
Atenolol	Group 2
Metoprolol	Group 2
Nadolol	Group 2
Propranolol	Group 1
Timolol	Group 1
Calcium Entry Blockers	
Diltiazem	Group 3a
Nimodipine	Group 2
Nicardipine	No controlled clinical trials
Verapamil	Group 2
Neurostabilizers	
Divalproex sodium	Group 1

Guidelines for Selected Prophylactic Therapies in the Treatment of Migraine (see Table 4.2 in the original guideline document for doses and clarifications)	
MEDICATION	US HEADACHE CONSORTIUM GUIDELINES
Gabapentin	Group 2
Tiagabine	Group 3a
Topiramate	Meets Group 1 criteria based on evidence not available at time of publication of Guidelines
NSAIDs	
Acetylsalicylic acid	Group 2
Celecoxib	No controlled clinical trials
Fenoprofen	Group 2
Flurbiprofen	Group 2
Ketoprofen	Group 2
Nabumetone	Group 5
Naproxen	Group 2
Rofecoxib*	No controlled clinical trials
Tricyclic Antidepressants	
Some drugs in this category have not been studied in controlled clinical headache trials, although clinical experience shows good effect in selected patients. Cost and potential for side effects should be considered.	
Nonsedating: Desipramine	Group 3a
Nonsedating: Protriptyline	Group 3a
Sedating: Amitriptyline	Group 1
Doxepin	Group 3a
Imipramine	Group 3a
Nortriptyline	Group 3a
Serotonin Reuptake Inhibitors	
Fluoxetine	Group 2
Fluvoxamine	Group 3a
Paroxetine	Group 3a
Sertraline	Group 3a
Other Antidepressants	
Bupropion	Group 3a
Nefazodone	No controlled clinical trials
Trazodone	Group 3a
Venlafaxine	Group 3a
Special-Use Therapies	
Methylergonovine	Group 3b
Phenobarbital 40 mg, ergotamine tartrate 0.6 mg, and belladonna alkaloids (bellafoline) 0.2 mg	No controlled trials
Cyproheptadine	Group 3a
Methysergide	Group 4

Guidelines for Selected Prophylactic Therapies in the Treatment of Migraine (see Table 4.2 in the original guideline document for doses and clarifications)	
MEDICATION	US HEADACHE CONSORTIUM GUIDELINES
Monoamine oxidase inhibitor (MAOI): Phenelzine requires intensive patient education and cooperation	Group 3b
Botulinum toxin type A	
Feverfew	Group 2
Magnesium	Group 2
Petasites hybridus extract	2 placebo controlled trials
Riboflavin (vitamin B_2)	Group 2

*On September 30, 2004, Vioxx (rofecoxib) was withdrawn from the U.S. and worldwide market due to safety concerns of an increased risk of cardiovascular events. See the U.S. Food and Drug Administration (FDA) Web site for more information.

Beta-blockers

The beta-adrenergic blockers are the most thoroughly studied and most widely used of all the migraine preventive agents. Generally, beta-blockers are 60 to 80% effective in reducing the frequency of attacks by more than 50%. The evidence is best for propranolol and timolol, both approved by the Food and Drug Administration (FDA) for migraine prophylaxis. Agents with partial agonist activity have not been shown to be effective in migraine prevention. The choice of beta-blocker should be based on specific properties such as beta-1 selectivity, convenience of the drug formulation, and idiosyncratic drug effectiveness. Combined or alternate trials of beta-blockers should be considered before giving up on treatment. Common side effects include fatigue, light-headedness, insomnia, bradycardia or exercise intolerance, depression, and sexual dysfunction. Use of beta-blockers should be avoided in patients with depression, asthma, severe cardiovascular disease, insulin-dependent diabetes mellitus, and Raynaud's disease.

Antidepressants

Antidepressants are also widely prescribed for migraine, despite the absence of FDA approval for their use in this setting. The tricyclic antidepressants, particularly amitriptyline, have long been established as extremely efficacious agents. They are inexpensive, are generally dosed once daily at bedtime, and offer advantages for patients with coexistent depression, insomnia, tension-type headache, or fibromyalgia. Drowsiness, weight gain, and dry mouth may limit their use, and they should be avoided in patients with cardiac conduction deficits. Several of the tricyclic agents are more activating, compared with those that are more sedating, and they should be taken in the morning, if possible.

Nontricyclic antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs) and venlafaxine and bupropion, have no established efficacy in migraine prevention. However, they are included among the agents found to be effective through clinical experience, and they can be particularly helpful in the presence of

comorbid anxiety or mood disorders. Common adverse events include sedation or insomnia, nausea, and sexual dysfunction.

Monoamine oxidase inhibitors (MAOIs), such as phenelzine, may be effective in selected cases. A tyramine-reduced diet is essential when MAOIs are used, and drug interactions (with selective serotonin reuptake inhibitors, meperidine, and certain triptans) limit their utility.

Calcium Antagonists

Although calcium antagonists are relatively popular because of their limited adverse events, they do not possess the established efficacy of the aforementioned drug classes. Verapamil and nimodipine exhibit the best efficacy data. Dizziness or hypotension, constipation, flushing, and edema are among the most common side effects.

Neurostabilizers

Neurostabilizers are relatively new in migraine prophylaxis and are becoming increasingly popular. Divalproex sodium has the most established efficacy through controlled clinical trials. Accumulating evidence indicates that topiramate is in the same general range of efficacy and tolerability as divalproex sodium. As with the other drug classes in migraine prophylaxis, the neurostabilizers may be used at doses lower than would be prescribed for other clinical uses. Typical doses are between 500 and 1,500 mg. Neural tube defects have been reported with divalproex sodium, and it is contraindicated in pregnant women or women at risk of pregnancy. Many specialists recommend providing folic acid when prescribing valproate for women of childbearing potential, although there is no evidence that folic acid prevents neural tube defects.

More recently, topiramate has been approved as a prophylactic agent for migraine. Most headache specialists recommend starting with a low dose (15 to 25 mg) and increasing the dose by 25 mg at weekly intervals until a dose of 100 to 200 mg is achieved. Occasional patients require higher doses. Topiramate has been associated with weight loss, which makes it an attractive option for appropriately selected patients.

Numerous other antiepileptic drugs are currently being investigated for use in migraine prophylaxis. The adverse events and cautions associated with this class of drugs vary, and they will need to be clarified based on the characteristics of each individual product.

Nonsteroidal Agents

The nonsteroidal anti-inflammatory drugs (NSAIDs) have modest efficacy in migraine prevention. Gastrointestinal side effects (erosive gastritis, peptic ulcer disease) and concerns over renal adverse events have limited their use in migraine prevention. More recently, the selective cyclooxygenase-2 (COX-2) agents have garnered interest as potential alternatives.

Other Agents

Three alternative therapies have efficacy data that place them in Group 2 (medications with efficacy suggesting only "modest" improvement and mild to moderate adverse events) of agents ranked by the US Headache Consortium: feverfew, magnesium (400 to 800 mg/day), and riboflavin (vitamin B2, 400 mg/day). Novel anticonvulsants, leukotriene antagonists, and botulinum toxin have all been the focus of recent clinical research.

Combination Therapy

Combination therapy may exhibit clinical efficacy as indicated by experience or expert consensus, but no evidence is available to support polypharmacy for migraine prophylaxis. Nevertheless, certain patients seem to benefit from treatment with multiple agents, influencing migraine through varied mechanisms. The most commonly used combinations are beta-blockers with tricyclic antidepressants or anticonvulsants with antidepressants. Combining methylergonovine with a vasodilator, such as a calcium channel blocker, to decrease side effects has been advocated. Some clinicians cautiously use the combination of phenelzine and amitriptyline in patients with headache refractory to treatment. Patients whose headaches do not respond to single agents in the first tier of drugs from the US Headache Consortium guidelines should be considered for referral to a physician who specializes in headache.

Certain acute medications should be used with caution when prescribing preventive medications. Ergotamine, dihydroergotamine, and sumatriptan can potentially enhance vasospastic properties in the presence of methysergide or methylergonovine. Moreover, because MAOIs decrease the first-pass metabolism of triptans (other than almotriptan, eletriptan, frovatriptan and, naratriptan), increasing their half-lives, their use with triptans should be avoided. Similarly, meperidine, tramadol, dextromethorphan, and sympathomimetics can be potentially lethal when added to MAOIs and may result in serotonin syndrome or hypertensive crisis.

Comorbid Conditions

Comorbid diseases can present certain therapeutic opportunities. For example, when a patient presents with migraine and hypertension and/or angina, beta-blockers or calcium channel blockers may be an effective choice for all conditions. For patients with migraine and depression or anxiety, the use of antidepressants should be considered. Alternatively, for patients with migraine and epilepsy, anticonvulsants such as divalproex sodium offer unique advantages.

Conversely, in individuals with more than one disease, certain medications may be contraindicated. For example, beta-blockers should be used with care in depressed patients. Tricyclic antidepressants, neuroleptics, and sumatriptan may lower the seizure threshold and should be used with caution in patients with epilepsy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

In addition to incorporating the US Headache Consortium's recommendations, the conclusions reflect clinical experience and the most recent medical literature.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Minimization of migraine symptomatology, reduced disability, and improved quality of life

POTENTIAL HARMS

- Common side effects of beta-blockers include fatigue, light-headedness, insomnia, bradycardia or exercise intolerance, depression, and sexual dysfunction. Use of beta-blockers should be avoided in patients with depression, asthma, severe cardiovascular disease, insulin-dependent diabetes mellitus, and Raynaud's disease.
- Drowsiness, weight gain, and dry mouth may limit the use of tricyclic antidepressants, and they should be avoided in patients with cardiac conduction deficits. Several of the tricyclic agents are more activating, compared with those that are more sedating, and they should be taken in the morning, if possible.
- Common adverse events of selective serotonin reuptake inhibitors (SSRIs) include sedation or insomnia, nausea, and sexual dysfunction.
- Monoamine oxidase inhibitors (MAOIs), such as phenelzine, may be effective in selected cases. A tyramine-reduced diet is essential when monoamine oxidase inhibitors are used, and drug interactions (with selective serotonin reuptake inhibitors, meperidine, and certain triptans) limit their utility.
- Although calcium antagonists are relatively popular because of their limited adverse events, they do not possess the established efficacy of the aforementioned drug classes. Verapamil and nimodipine exhibit the best efficacy data. Dizziness or hypotension, constipation, flushing, and edema are among the most common side effects.
- The nonsteroidal anti-inflammatory drugs (NSAIDs) have modest efficacy in migraine prevention. Gastrointestinal side effects (erosive gastritis, peptic ulcer disease) and concerns over renal adverse events have limited their use in migraine prevention.
- Certain acute medications should be used with caution when prescribing preventive medications. Ergotamine, dihydroergotamine, and sumatriptan can potentially enhance vasospastic properties in the presence of methysergide or methylergonovine. Moreover, because monoamine oxidase inhibitors decrease the first-pass metabolism of triptans (other than almotriptan, eletriptan, frovatriptan and, naratriptan), increasing their half-lives, their use with triptans should be avoided. Similarly, meperidine, tramadol, dextromethorphan, and sympathomimetics can be potentially lethal when

added to monoamine oxidase inhibitors and may result in serotonin syndrome or hypertensive crisis.
- Weight gain and alopecia are possible with divalproex sodium. Polypharmacy with other antiepileptic drugs may increase risk of hepatic complications in very young children. Divalproex sodium may cause pancreatitis and polycystic ovaries. Use with caution in women of childbearing potential.
- Topiramate may cause renal stones and transient paresthesias. If bicarbonate is reduced, there is a risk of metabolic acidosis.
- Significant food and drug interactions can occur with monoamine oxidase inhibitors. Ingestion of large amounts of tyramine may result in hypertensive crisis, myocardial infarction, or cerebrovascular accident (CVA).
- Tricyclic antidepressants, neuroleptics, and sumatriptan may lower the seizure threshold and should be used with caution in patients with epilepsy.

CONTRAINDICATIONS

CONTRAINDICATIONS

Neural tube defects have been reported with divalproex sodium, and it is contraindicated in pregnant women or women at risk of pregnancy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Drug therapy is constantly evolving as new research, clinical trials, case reports, and opinions are published. Many of the drugs recommended in these guidelines are not approved by the US Food and Drug Administration (FDA) for treatment of headache, nor are they necessarily the same as those therapies recommended by the manufacturer for labeled indications. Their use in headache, however, may be supported by the scientific literature and by the authors' clinical experiences. While efforts have been made to ensure accuracy, the authors and publisher do not assume responsibility for the consistent updating of available information for these guidelines, nor for any errors or omissions, nor for any consequences thereof. The onus is on the practitioner to evaluate recommendations in light of the clinical condition of the patient and recent medical literature. The authors advise the practitioner to consult other sources, especially the manufacturers' warnings and precautions, before prescribing any drug with which they are unfamiliar. Practitioners are also advised that while these guidelines will address the needs of many patients, there will be circumstances calling for exceptions to these recommendations.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Chart Documentation/Checklists/Forms
Foreign Language Translations
Patient Resources
Slide Presentation
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Kaniecki R, Lucas S. Treatment of primary headache: preventive treatment of migraine. In: Standards of care for headache diagnosis and treatment. Chicago (IL): National Headache Foundation; 2004. p. 40-52. [6 references]

ADAPTATION

Portions of the guideline were adapted from the American Academy of Neurology (AAN) & US Headache Consortium's evidence-based guidelines for migraine headache: behavioral and physical treatments 2000. (Available at: http://www.neurology.org/cgi/reprint/55/6/754.pdf).

DATE RELEASED

2004

GUIDELINE DEVELOPER(S)

National Headache Foundation - Private Nonprofit Organization

SOURCE(S) OF FUNDING

National Headache Foundation

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: Robert Kaniecki, MD, and Sylvia Lucas, MD, PhD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: None available

Print copies: Available from the National Headache Foundation, 820 N. Orleans, Suite 218, Chicago, IL 60610; Phone: (888) NHF-5552; Web address: www.headaches.org

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The complete headache chart. Chicago (IL): National Headache Foundation (NHF); 2 p. Electronic copies available in Portable Document Format (PDF) from the National Headache Foundation Web site
- National Headache Foundation fact sheet. Chicago (IL): National Headache Foundation (NHF); 2004 Oct. 2 p. Electronic copies available in Portable Document Format (PDF) from the National Headache Foundation Web site.
- Migraine prevention screening tool. Chicago (IL): National Headache Foundation (NHF). Electronic copies available from the National Headache Foundation Web site.
- Advances in migraine prophylaxis. Current state of the art and future prospects. Continuing medical education. Chicago (IL): National Headache Foundation (NHF); 2001. 10 p. Electronic copies available in Portable Document Format (PDF) from the National Headache Foundation Web site.

Print copies: Available from the National Headache Foundation, 820 N. Orleans, Suite 218, Chicago, IL 60610; Phone: (888) NHF-5552; Web address: www.headaches.org

PATIENT RESOURCES

The National Headache Foundation (NHF) has created a variety of educational resources for patients, including informative brochures, a patient diary for migraines, Power Point presentations, and patient guides; many of these resources are available in both Spanish and English. Some of these items are available as print copies for purchase through the NHF online store. Electronic

versions of other resources are available through the consumer education section of the NHF Web site.

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Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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